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A Randomized Trial Comparing the Cardiac Rhythm Safety of Moxifloxacin vs Levofloxacin in Elderly Patients Hospitalized With Community-Acquired Pneumonia*

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Context: **Antimicrobial cardiac safety is of particular concern during the treatment of community-acquired pneumonia (CAP) in elderly patients, due to the presence of comorbid conditions and the use of multiple medications that may individually or synergistically affect cardiac repolarization.**

Study objective: **To assess the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with CAP.**

Design and setting: **Prospective, randomized, double-blind trial conducted at 47 hospitals in the United States.**

Patients: **Subjects ≥ 65 years old with clinical signs/symptoms of CAP requiring initial parenteral therapy, including those with comorbidities. The safety population included 394 patients: 51.3% male; 85.3% white; mean age, 77.8 years. Two-thirds of the patients were > 75 years old, and 74.1% had a history of cardiac disease.**

Interventions: **Patients received IV/oral moxifloxacin (400 mg qd) or IV/oral levofloxacin (500 mg qd) for 7 to 14 days. Safety evaluations included 72 h of digital continuous 12-lead Holter monitoring, 12-lead ECGs at baseline and at maximum serum concentration on day 3, and adverse events.**

Main outcome measures: **The primary safety end point was a composite of ventricular arrhythmia events based on Holter monitoring.**

Results: **Holter monitor data were available for 387 patients (192 receiving moxifloxacin and 195 receiving levofloxacin). Sixteen moxifloxacin-treated patients (8.3%) and 10 levofloxacin-treated patients (5.1%) had a primary composite cardiac event (p = 0.29); most events were nonsustained ventricular tachycardia (VT) [14 patients receiving moxifloxacin, 7.3%; and 10 patients receiving levofloxacin, 5.1%]. One moxifloxacin-treated patient had sustained monomorphic VT (> 30 s), and one levofloxacin-treated patient had *torsade de pointes*. Mean ± SD QTc (Fridericia formula) change on day 3 was + 6.4 ± 23.2 ms for moxifloxacin and – 2.5 ± 22.9 ms for levofloxacin (p = 0.04). No deaths clearly related to study drugs occurred during the observation period.**

Conclusions: **IV/oral moxifloxacin, although known to cause QTc interval prolongation, has a comparable cardiac rhythm safety profile to IV/oral levofloxacin in high-risk elderly patients with CAP.**

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Key words: ambulatory ECG monitoring; cardiac repolarization; cardiac safety; community-acquired pneumonia; elderly; levofloxacin; moxifloxacin; QTc interval

Abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; CI = confidence interval; H-12 = 12-lead ECG Holter monitor; PSI = Pneumonia Outcome Research Team severity index; SVT = supraventricular tachycardia; VT = ventricular tachycardia

Cardiac safety of antimicrobial agents is of particular concern in the elderly population in light of their frequent comorbid conditions and use of multiple medications that may either individually or synergistically affect cardiac repolarization. Prolongation of cardiac repolarization following the administration of certain drugs has been appreciated for more than a half a century.[1] Some drugs (*eg*, cisapride, terfenadine) have been documented, after marketing, to prolong the QTc duration and result in potentially life-threatening ventricular tachyarrhythmias and were withdrawn or were restricted from marketing. These may include a polymorphic ventricular tachycardia (VT) known as *torsade de pointes* or "twisting of the points."[1] While lengthening of the QTc interval is considered a surrogate for increased risk of cardiac adverse events, the presence of a long QTc interval does not always predict ventricular

arrhythmias or *torsade de pointes*. Furthermore, accurate assessment of drug-associated QT prolongation is complicated by the fact that there is a large degree of spontaneous daily QTc variation observed even in normal subjects.[2]

Risk of QTc interval prolongation has been associated with different classes of antibiotics, such as macrolides and fluoroquinolones.[3–10] Fluoroquinolone-induced QTc prolongation raised concern following reports of fatal and nonfatal cardiac arrhythmias linked with sparfloxacin administration and more recently grepafloxacin.[7] Additional focus on the cardiac safety of fluoroquinolones was generated following the withdrawal of grepafloxacin from the US market in 1999, secondary to reports *of torsade de pointes*.[8] Unfortunately, the potential for many antibiotics to induce QT prolongation is poorly characterized, as adequate ECG analyses were not performed with many agents during their premarket development. Furthermore, there are limited prospective cardiac risk data following the administration of agents that have a minimal QTc-prolonging effect (< 10 ms) in patients who are at high risk for cardiac events.

Elderly patients are at greater risk for adverse effects due to underlying diseases and concomitant medications. Thus, the objective of this study was to evaluate whether the fluoroquinolones—moxifloxacin or levofloxacin—are associated with an increased potential to induce cardiac adverse events in this high-risk population. The efficacy and general safety data from this trial have been reported previously.[11] Levofloxacin was chosen as the comparator agent, as it is not generally associated with QTc interval prolongation. The inclusion of levofloxacin in this trial also permits a more thorough evaluation of this fluoroquinolone, as it has not been subjected to rigorous cardiac monitoring due to its introduction to the market prior to new guidance requiring more thorough evaluation of drug-induced QTc prolongation.

The primary goal of the current trial was to compare, by means of 72 h of digital 12-lead ambulatory ECG (Holter) data, the cardiac safety of sequential IV/oral moxifloxacin vs sequential IV/oral levofloxacin in elderly hospitalized patients (aged ≥ 65 years) with community-acquired pneumonia (CAP) who required these agents as initial parenteral therapy. This study is also unique in carefully examining cardiac rhythm events during the therapy of CAP in hospitalized elderly patients.

Materials and Methods

Study Design and Participants

This trial was a prospective, double-blind, multicenter, comparative study conducted from November 2002 to April 2004 at 47 centers in the United States. The study was conducted in accordance with the Declaration of Helsinki. The internal review board of each institution approved the study protocol, and written informed consent was obtained from each patient prior to enrollment.

Elderly patients (≥ 65 years old) with clinical signs and symptoms of CAP who required initial parenteral therapy were considered for enrollment in the trial. Patients were eligible for participation if they had radiologically confirmed evidence of a new or progressive infiltrate(s) consistent with bacterial pneumonia and at least two of the following findings: productive cough with purulent or mucopurulent sputum/tracheobronchial secretions (≥ 25 polymorphonuclear neutrophils/low-power field on Gram stain) or change in the character of sputum (increased volume or purulence); dyspnea or tachypnea (respiratory rate > 20 breaths/min); rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever (oral temperature $\geq 38°C/100.4°F$, rectal temperature $\geq 39°C/102.2°F$, or tympanic membrane temperature $\geq 38.5°C/101.2°F$) or hypothermia (rectal or core temperature $< 35°C/95.2°F$); and WBC count $\geq 10{,}000/\mu L$ or $\geq 15\%$ immature neutrophils (bands), regardless of the peripheral WBC count, or leukopenia with a total WBC count $< 4{,}500/\mu L$.

Patients were not allowed to participate in the study if they met any of the following conditions: hospitalization for > 48 h before development of pneumonia; presence of end-organ damage or shock (systolic BP < 90 mm Hg and diastolic BP < 60 mm Hg) with need for vasopressors for > 4 h at the time of study entry; need for mechanical ventilation at study entry; implanted cardiac defibrillator; significant bradycardia with heart rate < 50 beats/min; severe hepatic insufficiency (Child-Pugh class C); renal impairment with a baseline measured or calculated serum creatinine clearance < 20 mL/min; uncorrected hypokalemia; known prolongation of the QTc interval or use of class IA or class III antiarrhythmics; systemic antibacterial therapy for > 24 h within 7 days of enrollment unless the patient was deemed to have therapy failure after receiving > 72 h of a nonfluoroquinolone antibiotic; mechanical endobronchial obstruction; known or suspected active tuberculosis or endemic fungal infection; neutropenia (neutrophil count $< 1{,}000$/mL); long-term therapy (≥ 2 weeks) with known immunosuppressant therapy; known HIV

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infection and a CD4 count < 200/μL; and history of tendinopathy with quinolones or known hypersensitivity to study drugs.

Randomization, Treatments, and Blinding

Patients were stratified into a mild-to-moderate (stratum 1) pneumonia group or severe (stratum 2) pneumonia group using American Thoracic Society (ATS) criteria.[12] Patients were also assessed using the Pneumonia Outcome Research Team severity index (PSI).[13] Assignment to one of the two drug therapy groups was in accordance with a random code that was computer generated by Bayer Pharmaceuticals Corporation (West Haven, CT). Separate random code lists with a block size of four were produced for the two strata. The random numbers for stratum 1 start with 000001; the random numbers for stratum 2 start with 001441. Random numbers for each stratum were selected in ascending order starting from the top of each list. In this double-blind trial, the pharmacist at each center kept the random code lists for that center and was responsible for initiating and maintaining the integrity of the blinding. Each patient was assigned to a random code by the pharmacist according to the sequence of his or her enrollment within the center.

Each patient was randomized to receive initially either IV moxifloxacin, 400 mg qd, or IV levofloxacin, 500 mg qd. Patients could be switched to oral therapy (moxifloxacin, 400 mg qd, or levofloxacin, 500 mg qd) after ≥ 2 days of IV therapy if they met *a priori* criteria, *ie*, improved on IV therapy, afebrile for ≥ 8 h, and tolerated oral food/fluids/medications without vomiting or diarrhea. Antimicrobial therapy was administered for a total of 7 to 14 days, and patients were followed up for a further 5 to 21 days after therapy.

The dose of levofloxacin was adjusted for patients with creatinine clearance values from 20 to 50 mL/min based on approved product labeling, *ie*, a 500-mg loading dose followed by 250 mg qd. Patients randomized to moxifloxacin did not require dose adjustments in the presence of renal insufficiency.

IV moxifloxacin and levofloxacin are formulated as uniquely colored infusions. It was therefore necessary to administer two infusions to each patient (*ie*, one active drug to which the patient was randomized and one placebo infusion) in order to maintain the blind. As such, each patient received two concomitant infusions for at least 2 days. The moxifloxacin infusion is yellow, and the placebo infusion was 0.9% normal saline solution with a multivitamin infusion (M.V.I.-12; Astra USA; Westborough, MA) added to match the color (0.4% solution). The levofloxacin infusion is also yellow, although less so than moxifloxacin, and 5% dextrose saline solution was used as the placebo plus multivitamin infusion added to match the color (0.2% solution).

Cardiac Rhythm Safety Assessment and Evaluation

Patients receiving at least one dose of study drug were included in the cardiac rhythm safety analysis (intent-to-treat population). Cardiac safety was assessed on the basis of digital Holter ECG recordings for a total of 72 h (see below).

Each patient had continuous monitoring of their cardiac rhythms by digital 12-lead ECG Holter monitor (H-12) [Mortara Instruments; Milwaukee, WI] for the first 72 h of study participation (days 1 to 3). The H-12 can serve as both a traditional Holter monitor to evaluate the presence and frequency of arrhythmias, and then in a different mode the individual continuous recording of 12-lead ECGs can be identified. Standard 12-lead digital ECGs thus were extracted from the H-12 before therapy and immediately after administration of the third dose of IV study drug. All ECG and Holter data were analyzed using a manual digital on-screen method at a validated central laboratory (eResearch Technology; Philadelphia, PA). QT intervals were corrected for heart rate using both the Fridericia and Bazett formulas.[14,15]

A critical events committee, consisting of two cardiologists (J. M. and J. P. D.) who were blinded to treatment assignment, independently evaluated and adjudicated all cardiac events reported by the investigators during the course of the study. Consensus was reached on all events.

The primary cardiac safety variable was based on a "primary composite score" derived from the 72 h of Holter monitor recording. These included the following: (1) cardiac arrest—fatal and nonfatal—including cases of ventricular fibrillation and asystole; (2) sustained monomorphic or polymorphic VT without cardiac arrest (> 30 s); and (3) nonsustained monomorphic VT (≥ 10 beats, ≤ 30 s) and nonsustained polymorphic VT (≥ 10 beats, < 30 s), including *torsade de pointes* (≥ 10 beats of changing morphology during the run with a long QTc interval). The primary safety variable was to be coded as 1 if the patient experienced any of the events described above or 0 if otherwise.

Secondary cardiac safety variables included a "secondary composite score": any occurrence of atrial fibrillation (> 120 beats/min) with rapid ventricular response; new-onset atrial fibrillation; any nonsustained supraventricular tachycardia (SVT) with a rate > 120 beats/min; new-onset sustained (> 60 s) SVT; third-degree atrioventricular block; long RR pauses (> 3 s in patients with sinus rhythm and > 5 s in patients with atrial fibrillation), and overall mortality.

Statistical Analysis

Demographic and baseline characteristics were summarized using means, SDs, medians, and quartiles for continuous data and frequency count for categorical variables. The two treatment groups were compared using a one-way analysis of variance for continuous variables or using a χ^2 test for categorical data.

The primary hypothesis of the trial was that the levofloxacin group would have a lower primary composite score than the moxifloxacin group. Specifically, the null hypothesis specified that the levofloxacin group had an incidence rate lower than the moxifloxacin group by at least 10%. If this null hypothesis of levofloxacin superiority could be rejected, the conclusion would be that moxifloxacin was noninferior to levofloxacin. A two-sided 95% confidence interval (CI) for the weighted difference between treatment groups in the rates of this primary safety end point was constructed, using Mantel-Haenszel weights reflecting disease severity. Only when the upper limit of a two-sided 95% CI for the weighted difference in death or drug-related cardiac adverse event rates was < 10% and the lower limit was < 0 was moxifloxacin concluded to be noninferior to levofloxacin.

A logistic regression model was also used to examine the contribution of non-drug-related, predefined risk factors (*eg*, gender, history of heart disease, COPD, hypoxia, left ventricle ejection fraction < 50%, hypomagnesemia, concomitant QTc-prolonging medications) to the occurrence of cardiac events. A retrospective *post hoc* analysis was used to test the treatment effect on the incidence of each individual primary and secondary cardiac adverse event, as well as ECG changes (*eg*, QTc interval duration) between the pretherapy and post-third IV dose readings in the two treatment groups. All p values < 0.05 were considered significant. Assuming the incidence rate of drug-related cardiac adverse events was 9% for both treatment groups and an upper limit of noninferiority of 10% for the difference between treatment groups, the study has 90% power based on 401 patients enrolled.

Results

The trial enrolled a total of 401 elderly patients, of whom 7 patients never received study medication (Fig 1). Accordingly, the intent-to-treat (safety) population comprised 394 patients (195 receiving moxifloxacin and 199 receiving levofloxacin). The mean duration of antimicrobial therapy was 9.1 ± 3.4 days for the moxifloxacin group and 9.0 ± 3.6 days for the levofloxacin group.

Demographic and baseline medical characteristics for the safety population are summarized in Table 1. All variables were well balanced between the two treatment groups with a preponderance of white patients (85.3%) and a mean age of 78 years. Notably, two thirds of patients in both treatment groups were > 75 years of age. More than half of the safety population had PSI scores of 3 to 5. A history of a cardiac disorder was reported in high rates for both treatment groups (71.8% for moxifloxacin and 76.4% for levofloxacin). Rates of specific cardiac comorbidities were similar between the two groups, with the exception that there were slightly more patients in the moxifloxacin group who had a history of ventricular arrhythmias and cardiac arrest than those in the levofloxacin group (5.1% for moxifloxacin vs 2.5% for levofloxacin, $p = 0.27$). The mean left ventricular ejection fraction was 53.7% for the moxifloxacin group and 53.5% for the levofloxacin group. Poor general health status at baseline was noted for 7.7% of moxifloxacin-treated patients and 10.1% of levofloxacin-treated patients.

Concomitant medications were classified according to the Anatomic Therapeutic Chemical classification system codes. Prevalence rates of concomitant medication use were 100% in both treatment groups. There were no differences in the prevalence of concomitant medication use between the two groups ($p = 0.672$). There was no treatment difference in each type of concomitant medication use ($p > 0.05$), except for anti-Parkinson drugs (4% for moxifloxacin and 11% for levofloxacin, $p = 0.01$). The three most commonly used concomitant medications were drugs for obstructive airway diseases (75% for moxifloxacin vs 66% for levofloxacin), antithrombotic agents (62% for moxifloxacin vs 60% for levofloxacin), and drugs for acid-related disorders (59% for

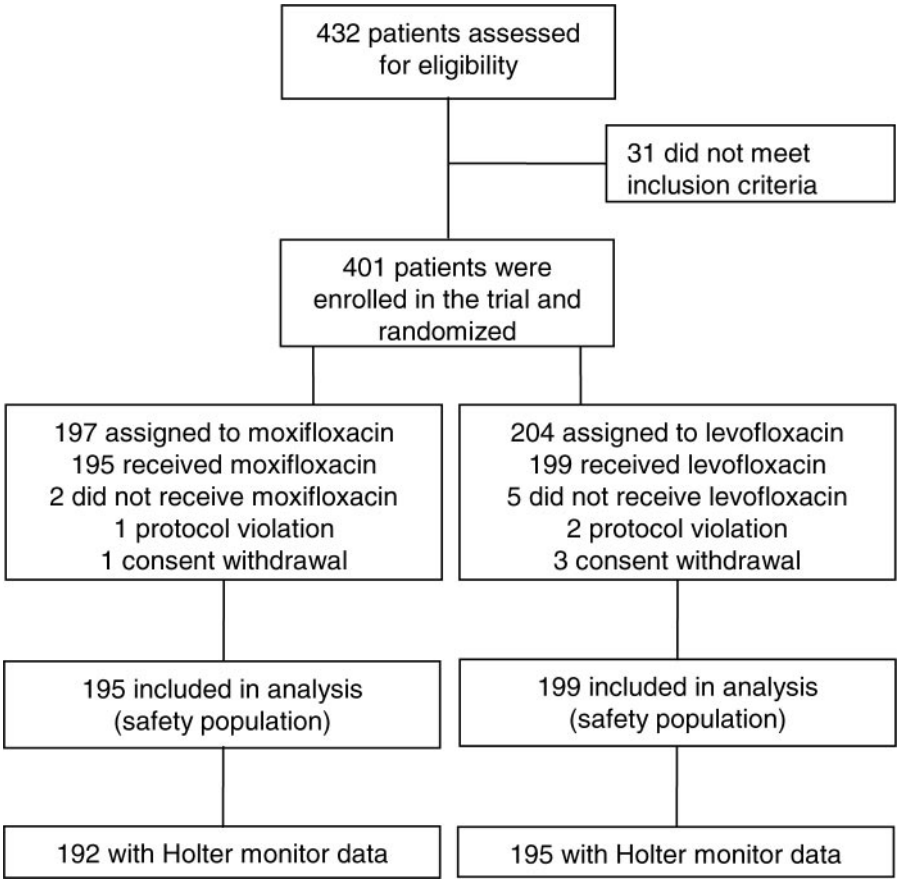

Figure 1. Profile of the trial and patient flow.

Table 1—*Demographic and Medical Characteristics (Safety Population)

Characteristics	Moxifloxacin (n = 195)	Levofloxacin (n = 199)
Male gender	100 (51.3)	102 (51)
Race		
White	166 (85.1)	170 (85.4)
Black	15 (7.7)	13 (6.5)
Hispanic	14 (7.2)	14 (7.0)
Asian	0	2 (1.0)
Mean age ± SD (range), yr	78.1 ± 7.5 (54–95)	77.5 ± 7.7 (55–98)
ATS severity, severe†	33 (16.9)	37 (18.6)
PSI score		
Missing	30 (15.4)	37 (18.6)
1	3 (1.5)	0
2	29 (14.9)	25 (12.6)
3	54 (27.7)	25 (12.6)
4	65 (33.3)	74 (37.2)
5	14 (7.2)	12 (6.0)
Selected comorbidities		
Cardiac disorders, any	140 (71.8)	152 (76.4)
Diabetes mellitus	52 (26.7)	63 (31.7)

*Data are presented as No. (%) unless otherwise indicated. All p values for treatment differences were nonsignificant (> 0.05).
†Per 2,001 ATS guidelines.[12]

moxifloxacin vs 62% for levofloxacin). Seventy-nine percent of the moxifloxacin-treated patients and 78% of the levofloxacin-treated patients had used medications in the cardiovascular system.

The mortality rates during the observation period were 7.7% (n = 15) in the moxifloxacin group and 5.5% (n = 11) in the levofloxacin group. Thirteen of those deaths (50%) occurred > 7 days after the last dose of study drug was received: nine moxifloxacin-treated patients and four levofloxacin-treated patients. None of the deaths were considered by the investigator to be related to the study drug, with the majority being due to underlying comorbid diseases. There were only two deaths reported during study drug therapy/Holter monitoring period; one of these was a fatal cardiac arrest (described below). The remaining patient died of worsening COPD.

Primary Safety Composite Variable

Holter data were available for 387 patients in the safety population, as 7 patients (3 receiving moxifloxacin and 4 receiving levofloxacin) did not have data recorded (Fig 1). Sixteen moxifloxacin-treated patients (8.3%) and 10 levofloxacin-treated patients (5.1%) had a primary composite cardiac safety event, the majority of which were nonsustained VT ≥ 10 beats (14 for moxifloxacin and 10 for levofloxacin) (95% CI, – 1.8 to 8.2; p = 0.49; Table 2). It should be noted that one patient in the moxifloxacin group had both VT > 30 s and VT ≥ 10 beats. While most nonsustained VT events were determined to have uniform morphology by the critical events committee blinded to treatment, one patient in the moxifloxacin group had multiple ectopic beat morphologies in an irregular run of slow VT, but not *torsade de pointes*, and one patient in the levofloxacin group

Table 2—*Primary and Secondary Cardiac Rhythm Safety End Points in Patients in the Safety Population Who Had Holter Data

End Points	Moxifloxacin (n = 192)	Levofloxacin (n = 195)	95% CI
Primary composite			
Sustained VT (> 30 s)	1 (0.5)	0	− 3.2 to 7.5
Nonsustained VT (≥ 10 beats, ≤ 30 s)	14 (7.3)	10 (5.1)	− 3.0 to 7.3
Uniform morphology	13 (6.8)	9 (4.6)	− 1.0 to 2.1
Multiple polymorphic VT morphologies	1 (0.5)	0	− 2.0 to 1.0
Torsade de pointes	0	1 (0.5)	− 1.0 to 2.1
Cardiac arrest	1 (0.5)†	0	− 1.0 to 2.1
Total patients	16 (8.3)	10 (5.1)	− 1.8 to 8.2
Secondary composite			
Atrial fibrillation (> 120 beats/min)	20 (10.4)	22 (11.3)	− 7.6 to 5.8
New-onset atrial fibrillation	10 (5.2)	9 (4.6)	− 4.2 to 5.4
Nonsustained SVT (> 120 beats/min)	125 (65.1)	125 (64.1)	− 9.0 to 11.0
New-onset SVT (> 60 s)	6 (3.1)	4 (2.1)	− 2.6 to 4.8
Third-degree atrioventricular block	2	0	− 0.9 to 3.0
Long RR pauses (> 3 s)	0	0	− 0.5 to 0.5
Total patients	141 (73.4)	140 (71.8)	− 7.8 to 11.0
Other Holter findings			
Nonsustained VT (> 3, < 10 beats)	69 (35.9)	69 (35.4)	− 9.5 to 10.6
Ventricular premature beats	183 (95.3)	188 (96.4)	− 5.6 to 3.4

*Data are expressed as the No. of patients (%) who experienced an event of that type. Each event is counted only once per patient. One moxifloxacin-treated patient had both VT > 30 s and VT ≥ 10 beats. All p values for treatment differences were nonsignificant (> 0.05).
†Resulting from respiratory failure following do-not-resuscitate order.

had an episode of actual *torsade de pointes*. One moxifloxacin-treated patient experienced monomorphic VT > 30 s that resolved spontaneously without treatment. The single episode of cardiac arrest in the moxifloxacin group occurred in a patient with end-stage COPD who died of respiratory failure with the ECG recording the agonal bradycardia and cardiac arrest. This patient had a do-not-resuscitate order, and care was withdrawn.

The frequencies of predefined risk factors that may initiate ventricular arrhythmia, in general, were higher in the moxifloxacin group vs those receiving levofloxacin. However, only a baseline history of hypothyroidism was significantly greater among moxifloxacin recipients (36 for moxifloxacin vs 22 for levofloxacin, $p = 0.04$). Notably, 60 moxifloxacin-treated patients and 60 levofloxacin-treated patients in the safety population received potentially QT-prolonging drugs. Several risk factors—male gender ($p = 0.04$), lower PSI score (score 2 and score 3) [$p = 0.01$], history of heart failure ($p = 0.0005$), and history of using QT-prolonging medication ($p = 0.02$)—were independently linked with higher rates of primary cardiac rhythm safety events. A subsequent multiple logistic regression model that included terms for these risk factors and for treatment revealed no significant correlation between the incidence of the primary cardiac rhythm safety events and treatment group after adjusting for these risk factors (data not shown).

Secondary Safety Composite Variable

Table 2 displays the rates of the five secondary safety composite variables for patients with Holter data. A large proportion of patients (73.4% for moxifloxacin and 71.8% for levofloxacin) experienced at least one of the five secondary cardiac rhythm safety events. The rates of each secondary event were very similar between the two treatment groups, with nonsustained SVT > 120 beats/min reported most often (approximately 65% per treatment group). The supraventricular arrhythmias documented represented a mixture of atrial fibrillation, sinus tachycardia, atrial flutter, and atrial tachycardia.

Other Holter Monitor Findings

Nonsustained VT < 10 beats was observed for approximately one third of patients in both treatment groups (35.9% for moxifloxacin and 35.4% for levofloxacin) [Table 2]. A total of 95.3% of moxifloxacin-treated and 96.4% of levofloxacin-treated patients had documented ventricular premature beats.

ECG Findings

Pretreatment ECGs were available for 320 patients in the safety population (161 receiving moxifloxacin and 159 receiving levofloxacin), and 117 patients (58 receiving moxifloxacin and 59 receiving levofloxacin) had both a valid pretreatment and day 3 ECGs. Nonpaired ECGs (50 for moxifloxacin and 46 for levofloxacin) and presence of atrial fibrillation (24 for moxifloxacin and 19 for levofloxacin) were the most common reasons for exclusion from this analysis.

For patients with valid paired ECGs, the mean QTc (Fridericia formula[14]) change on day 3 was $+ 6.4 \pm 23.2$ ms for moxifloxacin and $- 2.5 \pm 22.9$ ms for levofloxacin ($p = 0.04$). The corresponding mean QTc change using the Bazett formula[15] was $+ 5.3 \pm 23.7$ ms for moxifloxacin and $- 5.1 \pm 25.8$ ms for levofloxacin ($p = 0.03$).

Using the Fridericia formula, 8.6% (5 of 58 moxifloxacin-treated patients) had QTc values > 450 ms for men or > 470 ms for women, compared with 5.1% (3 of 59 levofloxacin-treated patients) [$p = 0.70$]. Corresponding values using the Bazett formula were 31% (18 of 58 patients) vs 16.9% (10 of 59 patients) [$p = 0.17$]. A QTc prolongation of 30 to 60 ms was observed for 15.5% (9 of 58 patients; Bazett formula) and 10.3% (6 of 58 patients; Fridericia formula) of moxifloxacin-treated patients, compared with levofloxacin: 6.8% (4 of 59 patients; Bazett formula; $p = 0.58$) and 6.8% (4 of 59 patients; Fridericia formula; $p = 1.0$), respectively. Only one patient in each group had a QTc increase > 60 ms. No patient in either treatment group with a prolonged QTc interval on the scheduled ECG recordings experienced an adverse cardiac event.

Discussion

The current prospective, double-blind, randomized trial rigorously assessed the cardiac rhythm safety of two different sequential IV/oral fluoroquinolone regimens—moxifloxacin vs levofloxacin—in hospitalized elderly patients with CAP who initially required parenteral therapy. This study observed that the incidence of cardiac events, primarily atrial fibrillation and nonsustained VT, during the treatment of elderly patients hospitalized with CAP was quite high. However, there were no significant differences in these findings comparing moxifloxacin (a drug known to increase QTc duration) to levofloxacin. Of additional clinical importance, there was no relationship between the occurrence of cardiac events and prolongation of the QTc interval dura-

tion. Notably, the study had no upper age limit for eligibility and broad eligibility criteria.

Few studies have evaluated the safety and efficacy of fluoroquinolones in elderly patients. Specifically, the goal of the study was to determine the cardiac rhythm safety profile of IV/oral moxifloxacin and IV/oral levofloxacin in elderly patients with CAP. Approximately 400 elderly patients participated, of whom two thirds were considered very elderly (> 75 years old) and nearly half were women. A large majority of patients had significant comorbid cardiac conditions (72% for moxifloxacin and 76% for levofloxacin) in addition to the current episode of CAP for which they received IV antimicrobial therapy. The major strengths of the current trial include the prospective, double-blind, randomized study design, inclusion of nursing home patients, the broad eligibility criteria with no upper age limit restriction, and inclusion of patients with multiple comorbidities. Thus, the trial evaluated a very high-risk patient population, one that might be at significant risk to experience a nonfatal or fatal cardiac adverse event as a result of fluoroquinolone administration.

The primary composite score analysis for cardiac events (*ie*, cardiac arrest [fatal or nonfatal], runs of VT > 30 s, and runs of nonsustained VT > 10 beats) revealed that moxifloxacin was statistically noninferior to levofloxacin. Of these, the most frequent cardiac event reported was VT > 10 beats, which occurred in 7.8% of moxifloxacin-treated patients vs 5.1% of levofloxacin-treated patients. The morphology was monomorphic in all but one moxifloxacin-treated patient (multiple atypical formed ectopy) and one levofloxacin-treated patient who had an episode of *torsade de pointes*, that lasted < 30 s. One additional moxifloxacin-treated patient had an episode of monomorphic VT lasting > 30 s before spontaneously reverting to normal sinus rhythm. Asystolic cardiac arrest occurred in a single moxifloxacin-treated patient during treatment and while on Holter monitoring but was judged to be a terminal event due to progressive respiratory failure. There is no evidence that these findings were due to the study drugs employed in this high-risk population, although their contribution cannot be excluded.

Notably, multiple logistic regression analyses that adjusted for risk factors for ventricular arrhythmia or prolongation of the QT interval confirmed the finding that moxifloxacin was not significantly more likely to cause a primary cardiac event compared with levofloxacin. Consistent cardiac rhythm safety results between moxifloxacin and levofloxacin were found for the secondary composite variable, albeit the vast majority of patients in both treatment groups experienced at least one event (> 70%). No treatment effect was noted, and the rate of these secondary events was probably due to the severity of pneumonia and comorbid diseases in this elderly population. It is also noteworthy that in elderly hospitalized patients with CAP, ventricular premature beats were very common, being observed in > 90% of patients in both treatment groups. The frequency of nonsustained VT < 10 beats also was relatively common (approximately 35% in each treatment group). However, because no baseline data were available for these latter observations, their relationship to clinical state or treatments could not be determined.

Few data are available in the literature regarding the occurrence of cardiac arrhythmias during a pneumonia episode. A unique aspect of the present study is that it captured the incidence of arrhythmias in elderly patients with pneumonia. Notably, these data from hospitalized elderly patients with CAP are similar to frequencies of nonsustained ventricular tachyarrhythmias in healthy elderly patients and elderly patients with congestive heart failure. One study[16] of 26 active, healthy men (70 to 81 years old) found an 11.5% rate of nonsustained VT detected by continuous ECG monitoring during their daily routine. Another study[17] reported an 87% postoperative incidence of repetitive ventricular arrhythmias during 3 days of continuous Holter monitoring after noncardiac surgery in patients with structural heart disease.

In addition, this study extends and confirms previous findings[10,18,19] that moxifloxacin increases the QTc interval by approximately 6 ms, whereas no increase in QTc duration was shown for levofloxacin. When assessing the clinical significance of the potential of moxifloxacin to induce QTc prolongation, with subsequent cardiac events, a number of factors must be considered. Factors independently associated with QTc prolongation include female gender, age ≥ 65 years, bradycardia, hypokalemia, hypocalcemia, hypomagnesemia, a history of cardiac disease, and concomitant QT-prolonging medications.[20–22] In general, drug-induced ventricular arrhythmias have been associated with QTc interval durations > 500 ms.[20–22] Increases from baseline of at least 30 ms in the QTc interval may be possibly drug related (a nonspecific change), whereas changes > 60 ms appear to be more specific in this regard.[1,2]

The clinical importance of noncardiac medications that induce a small (< 10 ms) QTc-prolonging effect remains controversial. Cardiac repolarization is controlled by a number of genetically determined ionic currents and is influenced by multiple extrinsic factors including ischemia, hypertrophy, heart failure, electrolyte imbalance, nervous system effects, and other metabolic and structural disorders. Most episodes of drug-in-

duced proarrhythmia are observed in settings in which the capacity for repolarization is reduced either genetically or through several simultaneously acting conditions that compromise the "repolarization reserve."[23–25]

The findings of this study must be interpreted in light of several limitations imposed by the study design. While these findings suggest that the incidence of cardiac events and QTc prolongation were not statistically or clinically different in hospitalized elderly patients administered moxifloxacin or levofloxacin, it may not be possible to generalize these findings to all elderly, hospitalized populations. For example, elderly patients who were already in an ICU prior to enrollment with CAP were excluded from the study because it would have been difficult to collect and interpret ECG data in this setting. Patients who had significant QTc prolongation ($\geq$ 500 ms) or bradycardia (heart rate $<$ 50 beats/min) at screening were also excluded from the study.

In conclusion, in this population of elderly patients with CAP who initially required IV therapy, sequential IV/oral moxifloxacin and levofloxacin were compared using 72 h of H-12 during IV drug administration and 12-lead ECGs at baseline and at maximum serum concentration on day 3. There was no difference between moxifloxacin and levofloxacin with respect to cardiac rhythm safety, as indicated by both primary and secondary safety composite variables. Nonsustained VT was the most frequently observed cardiac event after both moxifloxacin and levofloxacin therapy, with no immediate safety consequence. Overall, the observed new arrhythmia frequency in hospitalized elderly patients with CAP treated with the two fluoroquinolones studied does not exceed that expected in otherwise healthy elderly subjects and those with cardiac disease.

Appendix: The CAPRIE Study Group

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